DOI https://doi.org/10.17816/cardar634544

Unexplained cardiac arrest (idiopathic ventricular fibrillation): clinical and genetic characteristics

Svetlana M. Komissarova[1], Natalya N. Chakova[2], Nadiia M. Rineiska[1], Svetlana S. Niyazova[2], Tatyana V. Dolmatovich[2], Veronika Ch. Barsukevich[1], Larisa I. Plashchinskaya[1]

[1] "Cardiology" State Institution Republican Scientific and Practical Centre, Minsk, Belarus;
[2] Institute of Genetics and Cytology of Belarus National Academy of Sciences, Minsk, Belarus

ABSTRACT

AIM: The study was to evaluate the clinical and genetic characteristics of inherited arrhythmias in patients who survived unexplained cardiac arrest.

MATERIALS AND METHODS: 20 patients (10 male and 10 female) aged 15 to 55 years (median age 36 [28; 44] years) with documented VT/VF on ECG were observed for 3 years. The clinical and instrumental study included registration of 12-lead ECG, 24-hour Holter ECG, genealogical history collection and family history of sudden cardiac death with ECG assessment of all family members, transthoracic echocardiography, 2D Speckle Tracking echocardiography and cardiac magnetic resonance imaging to exclude structural myocardial changes. High-throughput sequencing (NGS) was utilized to search for mutations in genes linked to the onset of channelopathies and other inherited rhythm disorders.

RESULTS: In 4 (20%) of the 20 probands included in the study, likely pathogenic variants were identified (pathogenicity class IV), and in 7 (35%) patients, variants with unknown clinical significance (pathogenicity class III) in 10 genes associated with channelopathies (*KCNQ1*, *KCNH2*, *SCN5A*, *AKAP9*, *ANK2*, *SCN10*A, *RYR2)* and cardiomyopathies (*MYH7*, *JPH2*, *RBM20*). Several genetic variants were found in 3 cases. No significant genetic changes were detected in 9 (45 %) probands. The clinical diagnosis was established during the follow-up period and was verified due to the genetic testing in 5 (25 %) patients. From their ECGs, a prolonged *QTc* > 460 ms was found in 1 patient, Brugada pattern in 2 individuals, and a shortening of *QTc* up to 323 ms in 1 proband. Subclinical structural changes associated with cardiomyopathies were revealed in 2 patients. In 15 (75 %) patients, it was unfeasible to establish a distinct clinical phenotype. In 6 (30 %) probands, the diagnosis was clarified due to detected genetic variants.

CONCLUSION: Clinical manifestations and diverse genetic variants have been studied in patients who have survived unexplained cardiac arrest. In the course of genotyping patients who suffered unexplained cardiac arrest, genetic changes associated with LQTS were detected in 30 % of cases, while the *QTc* in most cases did not exceed 440 ms, which makes it difficult to establish a diagnosis at an early stage before the development of life-threatening arrhythmic events. The data from our study confirm the idea that in patients with idiopathic ventricular fibrillation, who have suffered unexplained cardiac arrest, cardiac channelopathy or subclinical manifestations of cardiomyopathy are commonly the cause. This phenomenon imposes a need for genetic testing in this category of patients.

Keywords: unexplained cardiac arrest; idiopathic ventricular fibrillation; genotypic and phenotypic diversity.

To cite this article

Komissarova SM, Chakova NN, Rineiska NM, Niyazova SS, Dolmatovich TV, Barsukevich VCh, Plashchinskaya LI. Unexplained cardiac arrest (idiopathic ventricular fibrillation): clinical and genetic characteristics. *Cardiac Arrhythmias.* 2024;4(2):5–18. DOI: https://doi.org/10.17816/cardar634544

Received: 23.07.2024 **Accepted:** 15.08.2024 **Published online:** 06.10.2024

DOI https://doi.org/10.17816/cardar634544

Необъяснимая остановка сердца (идиопатическая фибрилляция желудочков): клиническая и генетическая характеристика

С.М. Комиссарова[1], Н.Н. Чакова[2], Н.М. Ринейская[1], С.С. Ниязова[2], Т.В. Долматович[2], В.Ч. Барсукевич[1], Л.И. Плащинская[1]

[1] Республиканский научно-практический центр «Кардиология», Минск, Республика Беларусь;
[2] Институт генетики и цитологии Национальной академии наук Беларуси, Минск, Республика Беларусь

АННОТАЦИЯ

Цель исследования — оценить клиническую и генетическую характеристики наследственных аритмий у пациентов, переживших необъяснимую остановку сердца.

Материалы и методы. Обследовано 20 пациентов (10 мужского и 10 женского пола) в возрасте в возрасте от 15 до 55 лет (медиана возраста 36 [28; 44] лет) с документированной желудочковой тахикардией / фибрилляцией желудочков на электрокардиограмме, наблюдаемых в течение 3 лет. Клинико-инструментальное исследование включало: регистрацию электрокардиограмм в 12 отведениях, холтеровское мониторирование, сбор генеалогического анамнеза с оценкой электрокардиограмм всех членов семьи с выявлением случаев внезапной сердечной смерти в семье или наличия семейной формы заболевания, трансторакальную и 2D Speckle Tracking эхокардиографию и магнитно-резонансную томографию сердца для исключения структурных изменений миокарда. Поиск мутаций в кодирующих последовательностях генов, ассоциированных с развитием каналопатий и других наследственных нарушений ритма, проводили методом высокопроизводительного секвенирования.

Результаты. У 4 (20 %) из 20 включенных в исследование пробандов выявлены вероятно патогенные варианты (IV класс патогенности), у 7 (35 %) пациентов — замены с неизвестной клинической значимостью (III класс патогенности) в 10 генах, ассоциированных с каналопатиями (*KCNQ1*, *KCNH2*, *SCN5A*, *AKAP9*, *ANK2*, *SCN10A*, *RYR2)* и кардиомиопатиями (*MYH7*, *JPH2*, *RBM20*). Сочетание нескольких генетических вариантов обнаружено в 3 случаях. У 9 (45 %) из 20 пробандов значимых генетических изменений не выявлено. Клинический диагноз был установлен в период последующего наблюдения при комплексном обследовании и верифицирован в результате генетического обследования у 5 (25 %) пациентов. При анализе серии электрокардиограмм на одной из них выявлено удлинение интервала *QTc* > 460 мс; у 2 — паттерн Бругада; еще у 1 — укорочение интервала *QTc* до 323 мс. У 2 пациентов выявлены субклинические структурные изменения, ассоциированные с кардиомиопатиями. У 15 (75 %) пациентов не удалось установить явного клинического фенотипа. У 6 (30 %) из них диагноз был уточнен благодаря обнаруженным генетическим вариантам.

Заключение. Изучены клинические проявления и различные генетические варианты у пациентов, переживших необъяснимую остановку сердца. При генотипировании пациентов, перенесших необъяснимую остановку сердца, в 30 % случаев обнаруживали генетические изменения, ассоциированные с LQTS, при этом интервал *QTc* в большинстве случаев не превышал 440 мс, в связи с чем установление диагноза на ранней стадии до развития жизнеугрожающего аритмического события затруднено. Данные нашего исследования подтверждают идею о том, что у пациентов с идиопатической фибрилляцией желудочков, перенесших необъяснимую остановку сердца, в основе заболевания довольно часто лежат сердечная каналопатия или субклинические проявления кардиомиопатии, что диктует необходимость проведения генетического тестирования у этой категории пациентов.

Ключевые слова: необъяснимая остановка сердца; идиопатическая фибрилляция желудочков; генотипическое и фенотипическое разнообразие.

Как цитировать

Комиссарова С.М., Чакова Н.Н., Ринейская Н.М., Ниязова С.С., Долматович Т.В., Барсукевич В.Ч., Плащинская Л.И. Необъяснимая остановка сердца (идиопатическая фибрилляция желудочков): клиническая и генетическая характеристика // Cardiac Arrhythmias. 2024. Т. 4, № 2. С. 5–18. DOI: https://doi.org/10.17816/cardar634544

Рукопись получена: 23.07.2024 **Рукопись одобрена:** 15.08.2024 **Опубликована online:** 06.10.2024

INTRODUCTION

Sudden cardiac death (SCD) is the most common cause of mortality from cardiovascular diseases. Annually, 1–3 individuals per 100,000 people aged <35 years suddenly die [1, 2]. Studies have reveald that the frequent underlying cause of sudden cardiac arrest is inherited cardiac channelopathies [3, 4]. Autopsy findings of cardiomyopathy can be confirmed by postmortem genetic testing [5]. However, 30–40% of SCD cases in young adults remain unexplained [4, 6, 7]. Patients who survive cardiac arrest after administered cardiopulmonary resuscitation (CPR) may have genetic diseases for which genetic testing is mandatory. Such patients should undergo a comprehensive clinical evaluation focused on identifying the causative disease. If no aetiology is found, the patient is diagnosed with unexplained cardiac arrest (UCA) or idiopathic ventricular fibrillation (IVF). IVF is defined as UCA in a resuscitated patient showing no abnormalities on electrocardiogram (ECG) and in whom known cardiac, respiratory, metabolic, and toxicologic causes have been excluded by clinical evaluation [3, 4]. Studies have shown that IVF accounts for 5–7% of all out-of-hospital cardiac arrests [8].

According to the current European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on the state of genetic testing for cardiac diseases (EHRA/HRS/APHRS/LAHRS-2022) [9], genetic testing for diagnostically significant variants is recommended in UCA survivors in addition to a comprehensive clinical evaluation, and if detected, cascade screening of relatives is warranted [10].

In previous studies concerning the diagnostic use of postmortem genetic testing, a series of unexplained cardiac deaths in 26% of cases revealed the presence of allegedly pathogenic variants in genes associated with major channelopathies, including catecholaminergic polymorphic ventricular tachycardia (CPVT) (*RYR2* gene), long *QT* syndrome (LQTS) types 1–3 (*KCNQ1, KCNH2*, and *SCN5A* genes), and Brugada syndrome type 1 (*SCN5A* gene) [7]. Genetic screening of autopsy material from 302 individuals who died of sudden arrhythmic death syndrome was recently conducted. According to the 2015 American College of Medical Genetics and Genomics (ACMG) criteria, pathogenic and likely pathogenic variants in genes associated with channelopathies were identified in 11% of cases [11]. Additionally, pathogenic variants were identified in 2% of cases in genes associated with cardiomyopathies, indicating a structural cause of UCA that may have not been detected. The diagnostic yield increased by an average of 30% with the implementation of molecular genetic screening and clinical examination of family members [10, 11]. Genetic testing of UCA survivors using extended panels revealed the number of channelopathies and cardiomyopathies with an alleged pathogenic variant ranging from 3% to 27% [8, 12, 13].

The present study analyzed a cohort of patients with UCA caused by IVF who were successfully resuscitated and underwent implantation of cardioverter-defibrillator (ICD). Genetic alterations were assessed in these patients.

This study aimed to evaluate the clinical and genetic characterization of inherited arrhythmias in patients who survived UCA.

MATERIALS AND METHODS

Twenty patients (10 men, 10 women) aged 15–55 years with documented ventricular tachycardia (VT)/ventricular fibrillation (VF) on ECG were enrolled consecutively. The median follow-up period was 3 years.

Patients who had UCA with documented VT or VF requiring cardioversion or defibrillation, no left ventricular (LV) dysfunction (LV ejection fraction ⩾50%), and intact coronary arteries (no coronary stenosis >50%) were included. In contrast, patients with known causes of cardiac arrest ($n = 5$), including ECG diagnosis of LQTS (resting *QTc* >460 ms in men and 480 ms in women) or Brugada syndrome, hypertrophic cardiomyopathy, marked hypokalemia, and drug overdose, were excluded. Genetic testing, which was approved by the local ethics committee, was performed on all the study patients (minutes no. 2 of the meeting of the Bioethics Committee of the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus, dated June 8, 2021). All patients signed a voluntary informed consent to participate in the study.

Clinical and instrumental studies included a resting 12-lead ECG using the Intercard-3 recorder (Republic of Belarus), transthoracic echocardiography (TTE) using the IE-33 ultrasound system (Philips, USA), X-ray selective coronary angiography using Innova 3100 (General Electric, USA) and Siemens Artis Zee Cath/Angio System (Siemens, USA), or coronary CT scan (Siemens Somatom Force, Germany). Patients who met the enrollment criteria underwent further testing, including 24-hour Holter monitoring using Philips Zimed (Austria) and Oxford Medilog AR12 (UK) recorders, 2D Speckle Tracking TTE using Vivid 7 premium cardiac ultrasound system (General Electric, USA), and cardiac magnetic resonance imaging (MRI) using Magnetom Aera 1.5 T tomograph (Siemens, Germany) according to recent recommendations.

Mutations in the coding sequences of genes associated with channelopathies and other inherited cardiac arrhythmias were evaluated with high-throughput next-generation sequencing (NGS) using a MiSeq Gene Analyzer (Illumina, USA). Samples were prepared with the TruSight Cardio Sequencing Kit (Illumina, USA), which contains 174 genes associated with inherited cardiovascular diseases. Annotation of the sequencing results was conducted using the ANNOVAR software [14]. The clinical significance of new and previously

described genetic variants was evaluated according to the 2015 ACMG recommendations. [15]. The following factors were considered: the prevalence of the identified genetic variant in large population samples (Genome Aggregation Database [GnomAD]), localization in the gene and variant type, prediction of pathogenicity *in silico*, assessment of pathogenicity status in genetic databases (ClinVar, HGMD) and in peer-reviewed literature, availability of functional studies, and analysis of cascade screening data to elucidate variant segregation with disease within a family. Genetic variants classified as pathogenic (class V) and likely pathogenic (class IV) were considered diagnostically significant. Additionally, variants of uncertain significance (VUS; class III), which were predicted to be pathogenic *in silico* and whose frequency of occurrence in population databases (GnomaD) did not exceed 0.01%, were analyzed.

Statistical analysis was conducted using the StatSoft Statistica version 12.0 package and Microsoft Excel 2021. The quantitative data were represented by the median and quartiles in the form of *Me* [*LQ; UQ*], whereas the qualitative data were described by absolute values and percentages (*n* [%]).

RESULTS

Overall, 20 patients (10 women, 10 men; median age: 36 [28; 44] years) who had UCA caused by IVF and underwent resuscitation and ICD implantation were studied. Among the patients, 16 (80%) had a history of syncope. Moreover, 4 (20%) patients had close relatives with SCD (Table 1). The patients' clinical and instrumental characteristics are presented in Table 2.

Genotyping by NGS revealed likely pathogenic variants in 4 (20%) patients (Table 3). In 7 (35%) probands, variants of unknown clinical significance (pathogenicity class III) were detected in 10 genes associated with channelopathies (*KCNQ1, KCNH2, SCN5A, AKAP9, ANK2, SCN10A*, and *RYR2*) and cardiomyopathies (*MYH7, JPH2*, and *RBM20*). A combination of several genetic variants was found in three patients. No significant genetic changes were determined in 9 (45%) of 20 probands. Clinical diagnosis was established during the follow-up period by comprehensive examination and confirmed by genetic testing in 5 (25%) patients (codes 873c, 15m, 732, 799, and 642). Serial ECGs showed *QTc* interval prolongation >480 ms in one patient (code 873c), Brugada pattern in two patients (codes 732 and 799), and *QTc* interval shortening up to 323 ms in one patient (code 15m). Subclinical structural changes associated with cardiomyopathies were identified in two patients (codes 816 and 868c). In 15 (75%) patients, no clear clinical phenotype was established (codes 829, 586, 543, 642c, 590, 868c, 644, 647, 629, 612, 729, 805, 574, 648c, and 782). In 6 (30%) patients (codes 829, 586, 543, 642c, 590, and 868c), the diagnosis was clarified using the genetic variants detected.

LQTS-related genetic alterations were prevalent among patients with UCA caused by VF, occurring in 30% of cases. Proband 873c (female, 48 years old) exhibited *QTc* prolongation caused by a variant in the *KCNH2* gene (Fig. 1). The disease manifested at age 48 years with cardiac arrest, which was treated with resuscitation and subsequent ICD implantation. A series of ECGs obtained over the past year demonstrated no alterations in T wave morphology or *QTc* prolongation (420–440 ms). An ECG performed a year ago exhibited *QTc* prolongation of up to 482 ms. The patient had been suffering from syncope and presyncope for approximately 3 years. Based on the genotyping data, LQTS type 2 was diagnosed.

VUS in exons 15 and 38 of the *ANK2* gene, which encodes the adaptor protein ankyrin-B, were identified in two unrelated male probands (codes 543 and 586).

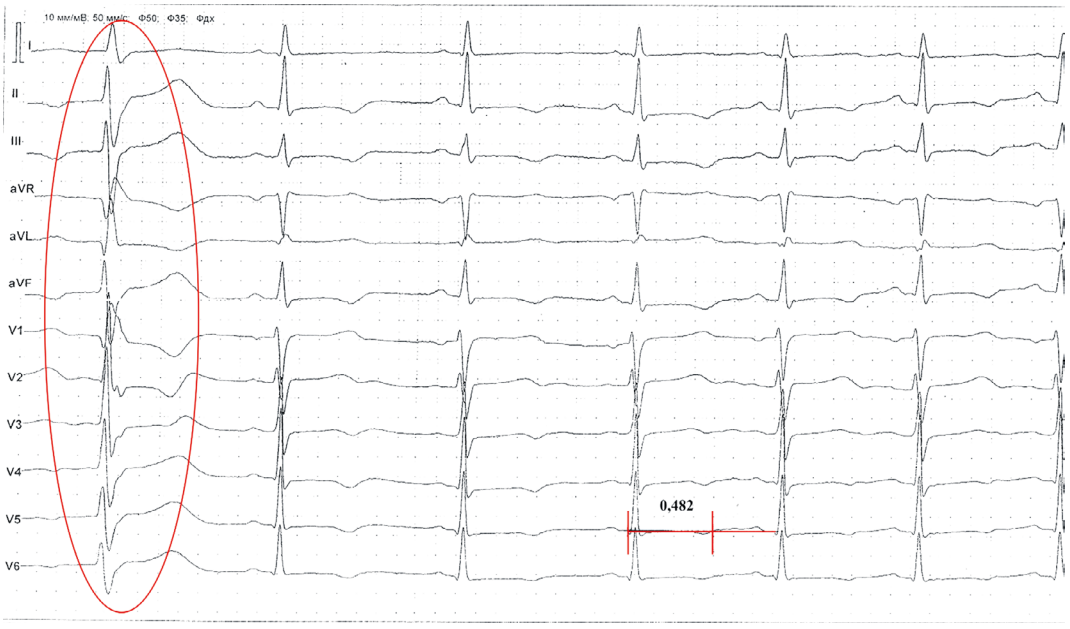

Fig. 1. 12-lead ECG of proband 873c. Prolonged QTc interval — 482 ms, ventricular premature beat (red ellipse)

Table 1. Clinical and genetic characteristics of patients with idiopathic ventricular fibrillation

Patient code	Age	Sex	Family history of SCD	History of syncope	*QTc* max	Gene (variant class)	Clarified diagnosis	Events/outcomes
873c	48	female	–	+	530	*KCNH2* (III–IV)	LQTS2	VF, CPR, ICD
829	44	female	–	+	380	*AKAP9* (III)	LQTS11	VF, CPR, ICD
586	33	male	–	+	445	*ANK2* (III)	LQTS4	VF, CPR, ICD
543	45	male	–	+	375	*ANK2* (III)	LQTS4	Recurrent VT/VF, ICD, electrical storms
15м	29	male	–	–	323	*KCNQ1* (III)	SQTS	VF, CPR, ICD
732	55	female	–	+	430	*SCN10A* (III)	BrS	VF, ICD
799	41	male	+	+	420	*SCN5A* (V) *JUP* (III)	BrS	VF, ICD
642c	15	male	–	+	450	*RYR2* (IV–V)	CPVT	VT/VF, CPR, ICD
590	21	male	–	–	374	*CACNA1C* (III)	IVF	VF, CPR, ICD
816	19	male	+	–	380	*RBM20* (IV) *MYH7* (III)	NDLVC	VF/EC
868c	36	female	–	+	410	*KCNH5* (III) *JPH2* (III)	IVF	VF, EC, ICD
644	46	female	–	+	460	not detected	IVF	VT/VF, ICD
647	46	male	–	+	477	not detected	IVF	VT/VF, ICD
629	40	female	–	+	478	not detected	IVF	VF, CPR, ICD
612	16	male	–	+	380	not detected	IVF	VF, CPR, ICD
729	44	female	–	+	405	not detected	IVF	VF, CPR, ICD
805	23	female	–	+	340	not detected	IVF	VF, CPR, ICD
574	30	female	+	+	450	not detected	IVF	VF, CPR, ICD
648c	36	female	+	+	448	not detected	IVF	VF, CPR, ICD
782	30	male	–	–	420	not detected	IVF	VF, CPR, ICD

Note: SCD — sudden cardiac death; VF — ventricular fibrillation; CPR — cardiopulmonary resuscitation; ICD — implantable cardioverter-defibrillator; VT — ventricular tachycardia; EC — electrical cardioversion; LQTS — long *QT* syndrome; SQTS — short *QT* syndrome; CPVT — catecholaminergic polymorphic ventricular tachycardia; IVF — idiopathic ventricular fibrillation; NDLVC — non-dilated left ventricular cardiomyopathy; BrS — Brugada syndrome.

DOI: https://doi.org/10.17816/cardar634544

Table 2. Clinical and instrumental characteristics of patients with unexplained cardiac arrest

Parameters	Group of patients with UCA (*n* = 20)
Clinical parameters	
Age at diagnosis, years, *Me* [*LQ*; *UQ*]	36 [28; 44]
Age of disease manifestation, years, *Me* [*LQ*; *UQ*]	35 [27; 41]
Gender, *n* (%)	
Female	10 (50)
Male	10 (50)
Family history of SCD, *n* (%)	4 (20)
Syncope, *n* (%)	16 (80)
Clinical phenotype, *n* (%)	
LQTS	4 (20)
SQTS	1 (5)
Brugada syndrome	2 (10)
CPVT	1 (5)
NDLVC	1 (5)
IVF	11 (55)
QTc max, *Me* [*LQ*; *UQ*]	420 [380; 450]
TTE parameters	
LV EF, %, *Me* [*LQ*; *UQ*]	58 [56; 63]
LAVI, mL/m^2,*Me* [*LQ*; *UQ*]	34 [30; 38]
LV EDD, mm, *Me* [*LQ*; *UQ*]	50 [48; 53]
LV ESD, mm, *Me* [*LQ*; *UQ*]	31 [30; 34]
LV EDV, mL, *Me* [*LQ*; *UQ*]	112 [106; 135]
LV ESV, mL, *Me* [*LQ*; *UQ*]	49 [36; 56]
PASP, mmHg, Me [LQ; UQ]	21 [20; 23]

Note: UCA — unexplained cardiac arrest; SCD — sudden cardiac death; LQTS — long *QT* syndrome; SQTS — short *QT* syndrome; CPVT — catecholaminergic polymorphic ventricular tachycardia; IVF — idiopathic ventricular fibrillation; NDLVC — non-dilated left ventricular cardiomyopathy; *QTc* — corrected *QT* interval; TTE — transthoracic echocardiography; LV EF — left ventricular ejection fraction; LAVI — left atrium volume index; LV EDD — left ventricular end-diastolic diameter; LV ESD — left ventricular end-systolic diameter; LV EDV — left ventricular end-diastolic volume; LV ESV — left ventricular end-systolic volume; PASP — pulmonary artery systolic pressure.

Both patients exhibited no aggravated family history and demonstrated *QTc* interval prolongation on ECG series (median *QTc*: 407.5 [375; 440] ms). Prior to the onset of VF, the patients experienced recurrent syncope requiring CPR and ICD implantation. Patient 543 (male, 43 years old) who had a p.Thr466Met substitution in the ANK2 gene developed polymorphic VT/VF controlled by an ICD multiple times during the 8-year follow-up, which led to ICD replacement 3 times. During the last 2 years, no recurrences of syncopal episodes and multiple ICD storms requiring CPR were noted. Considering the results of genotyping, the patients were diagnosed with IVF probably caused by mutations in the ankyrin gene.

In proband 829 (female, 44 years old) who showed a novel variant in the *AKAP9* gene, no family history of SCD and no *QT* interval prolongation on serial ECGs were recorded. The disease manifested at age 44 years with cardiac arrest caused by VF, which required CPR and ICD implantation. Frequent premature ventricular contractions and sustained and nonsustained paroxysms of VT were recorded during 24-hour Holter monitoring (Fig. 2). A comprehensive examination showed no structural myocardial abnormalities. Considering the genotyping data, VF was diagnosed due to the variant in the *AKAP9* gene. However, subsequent cascade screening of the proband's son (32 years old) and daughter (25 years old) using Sanger sequencing did not establish the pathogenic significance of the new variant, because both children were carriers of the same c.8747C>T substitution in the *AKAP9* gene, but had no ECG alterations and no other clinical manifestations. Owing to the incomplete penetrance of the disease and pathogenicity of the variant according to *in silico* prognostic predictors, regular follow-up with a cardiologist was recommended.

Cardiac arrest due to IVF and subsequent ICD implantation were recorded in four genotype-negative patients (codes 644, 647, 629, and 574) with borderline *QTc* values on ECG (median 465 [460; 477]). Moreover, two of the patients had a family history of SCD, indicating a hereditary nature of the disease (Table 1).

In 2 (10%) patients, the disease manifested with the development of IVF following CPR and ICD implantation; a Brugada pattern was detected on ECG at follow-up. Proband 799 (male, 41 years old) had a family history of SCD; his father died from SCD at age 28 years (Fig. 3). The proband experienced syncopal episodes unrelated to physical activity during the day and, eventually, cardiac arrest developed at night. ECG showed a spontaneous Brugada type 1 pattern. Hereinafter, no Brugada pattern was observed, and sinus rhythm with HR at 68 beats/min, *PQ* interval duration at 110 ms, *QTc* interval at 380 ms, and *QRS* at 120 ms was recorded. Genotyping revealed a likely pathogenic variant p.Glu48Lys in the *SCN5A* gene and an additional substitution in the *JUP* gene associated with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Cardiac MRI showed no structural myocardial changes nor evidence of ARVC. Considering the genotyping data, Brugada syndrome was diagnosed. Cascade screening in the proband's younger brother (31 years old) and daughter (10 years old) revealed a variant in the *SCN5A* gene. Neither had a substitution in the *JUP* gene, herewith the daughter having syncopal episodes and the younger brother being asymptomatic.

Patient 732 (female, 55 years old, no family history of SCD) who was admitted to the intensive care unit with cardiac arrest had a recorded VF and was subsequently implanted with an ICD. ECG showed a Brugada type 1 pattern (Fig. 4). Genotyping revealed a p.Asp1739Val substitution in the *SCN10A* gene encoding a neuronal sodium channel (Nav1.8), which has been associated with Brugada syndrome in recent whole-genome association studies. Phenotypic similarities have been demonstrated between patients with a *SCN10A* gene variant and *SCN5A* gene variants, including family history, presence of syncope, and spontaneous ECG pattern [16].

In patient 642c (male, 15 years old), the disease manifested at age 15 years with the development of cardiac arrest caused by polymorphic VT/VF (Fig. 5). CPR was performed, and a ICD was implanted for secondary prevention of SCD. Genotyping revealed a pathogenic mutation, c.14876G > A (p.Arg4959Gln, rs794728811), in the *RYR2* gene. Based on these results, CPVT was diagnosed. The mother of the proband was found

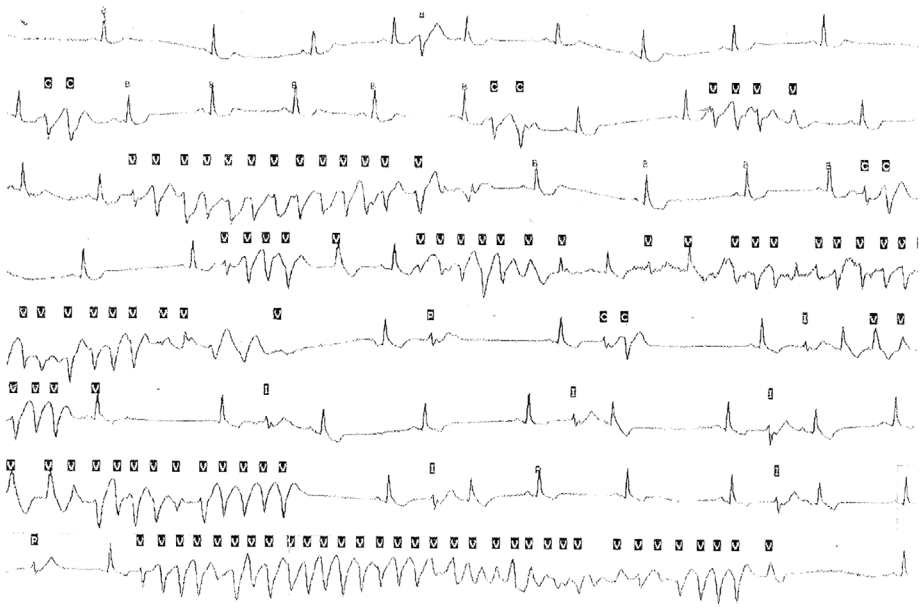

Fig. 2. 24-hour Holter ECG of patient 829. Ventricular premature beats and paroxysms of nonsustained ventricular tachycardia

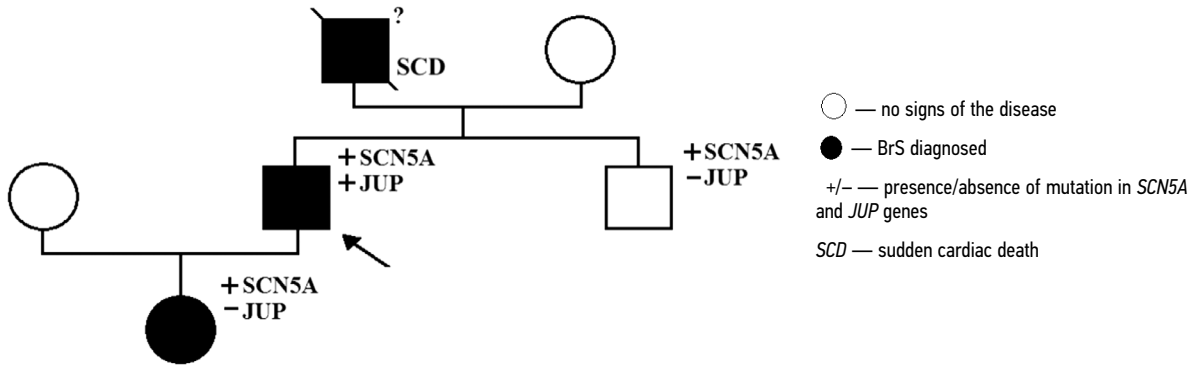

Fig. 3. Pedigree of the proband 799's family with mutations p.Glu48Lys in *SCN5A* gene and p.Ala143Thr in *JUP* gene. The proband is indicated by an arrow. Clinically affected individuals are indicated by the shaded symbols

Table 3. Genetic characteristics of variants in patients with idiopathic ventricular fibrillation

Patient code	Gene	Nucleotide substitution / Rs	Amino acid substitution	Variant class	MAF (GnomaD)
873c	*KCNH2*	c.2948C>T rs149955375	p.Thr983Ile	LP/VUS	0.00001983
829	*AKAP9*	c.8747C>T rs146648044	p.Thr2916Ile	VUS*	–
586	*ANK2*	c.9161C>G rs139007578	p.Ala3054Gly	VUS	0.00001363
543	*ANK2*	c.1397C>T rs786205722	p.Thr466Met	VUS	0.00005373
15м	*KCNQ1*	c.1831G>A rs147445322	p.Asp611Asn	VUS	0.000072
799	*SCN5A*	c.142G>A, rs199473048	p.Glu48Lys	LP	0.000039
	JUP	c.427G>A, rs375788626	p.Ala143Thr	VUS	0.00009858
732	*SCN10A*	c.5216 A>T, rs760863009	p.Asp1739Val	VUS	0.000014
642c	*RYR2*	c.14876G>A rs794728811	p.Arg4959Gln	P/LP	–
590	*CACNA1C*	c.5432_5433insCAACGCCAACATCAA rs765818401	p.S1811delinsSNANIN	VUS	0.000012
816	*MYH7*	c.4984C>T rs773977507	p.Arg1662Cys	VUS	0.000007955
	RBM20	c.2656-1G>A	splicing	LP*	–
868c	*JPH2*	c.1275C>A rs2145840509	p.Asp425Glu	VUS	–
	KCNA5	c.497A>C rs748629738	p.Asp166Ala	VUS	0.0001221

Note: * — new variant; P — pathogenic variant; LP — likely pathogenic; VUS — variants of uncertain significance; MAF — minor allele frequency.

to have the same mutation, which manifested clinically as presyncope and palpitations.

In patient 590 (male, 21 years old), a comprehensive clinical examination following cardiac arrest and resuscitation with subsequent ICD implantation revealed no structural abnormalities or ECG alterations. Genotyping identified a *CACNA1C* gene variant, which encodes the *L*-type calcium channel alpha subunit (CAV1.2). This variant is associated with channelopathies, namely, Timothy syndrome. However, no changes were detected on ECG, and no indications of syndactyly, cognitive impairment, facial dysmorphism, or other noncardiac characteristics suggestive of Timothy syndrome were observed.

Notably, variants in genes associated with the development of cardiomyopathy were detected in two patients with IVF. In patient 816 (male, 19 years old), who exhibited no myocardial structural abnormalities at the time of examination, variants in the *RBM20* and *MYH7* genes associated with various cardiomyopathies, including the dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy (NDLVC) phenotype, were detected on TTE and cardiac MRI. The patient had no obvious clinical phenotype during VF. A family history of SCD was noted; his mother developed the disease at age 33 years. At 2-year follow-up, 2D-Strain TTE showed a moderate decrease in global longitudinal strain (–13.6%) (Fig. 6), with no LV dilatation, confirming cardiomyopathy. Thus, the diagnosis of IVF was changed to NDLVC. In patient 868c (female, 36 years old), in the absence of myocardial structural abnormalities, variants in *JPH2* genes associated with cardiomyopathies and in *KCNA5* associated with familial atrial fibrillation were detected on TTE and cardiac MRI. No alterations of T wave morphology or prolonged *QTc* interval (*QTc*: 420–440 ms) were observed on ECG. No atrial fibrillation was determined in the patient's medical history or during 24-hour Holter monitoring. Moreover, no evidence of cardiomyopathy or cardiac channelopathy was found in the patient's family history. Currently, subclinical structural myocardial abnormalities are suspected in the patient, and further follow-up is required to confirm the diagnosis.

In a group of 20 patients with UCA and VF, the clinical phenotype was linked to genetic variants in 11 (55%) patients,

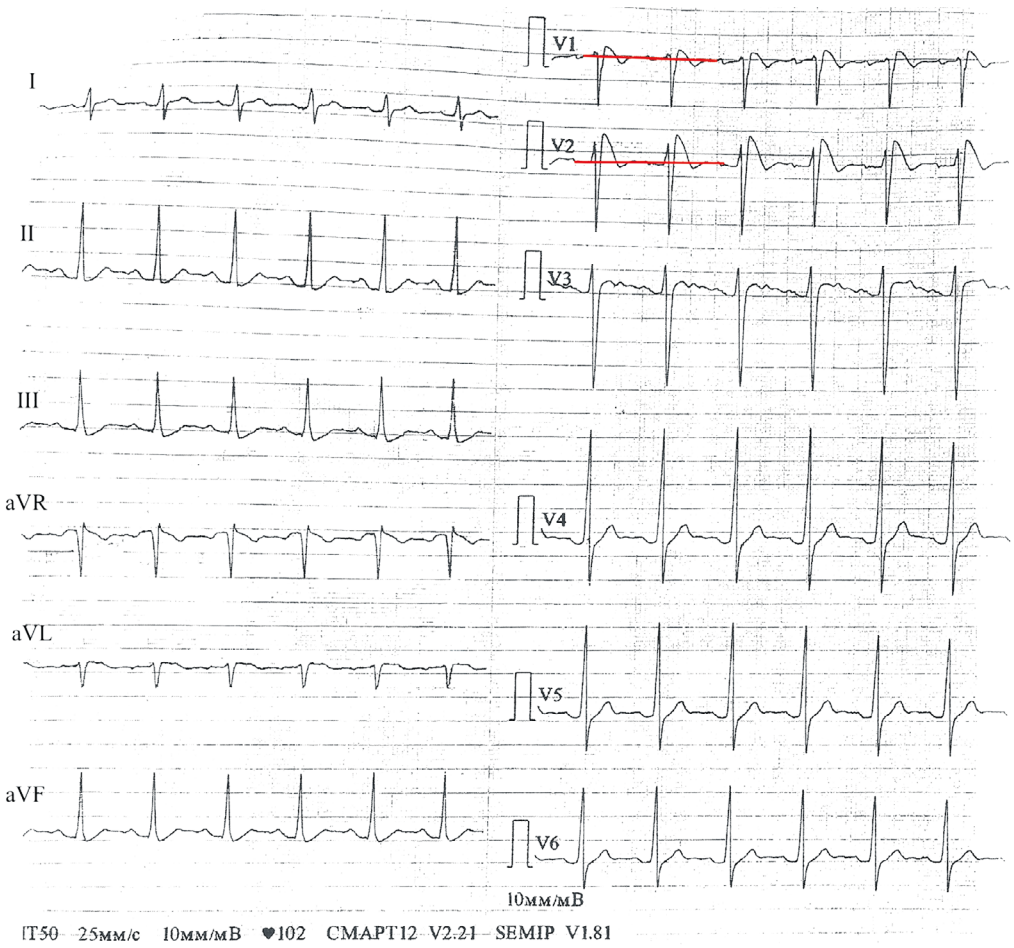

Fig. 4. 12-lead ECG of patient 732 with Brugada pattern type 1 ("coved"), showing a "vaulted" ST elevation of more than 2 mm in V1–V2, followed by a negative T-wave

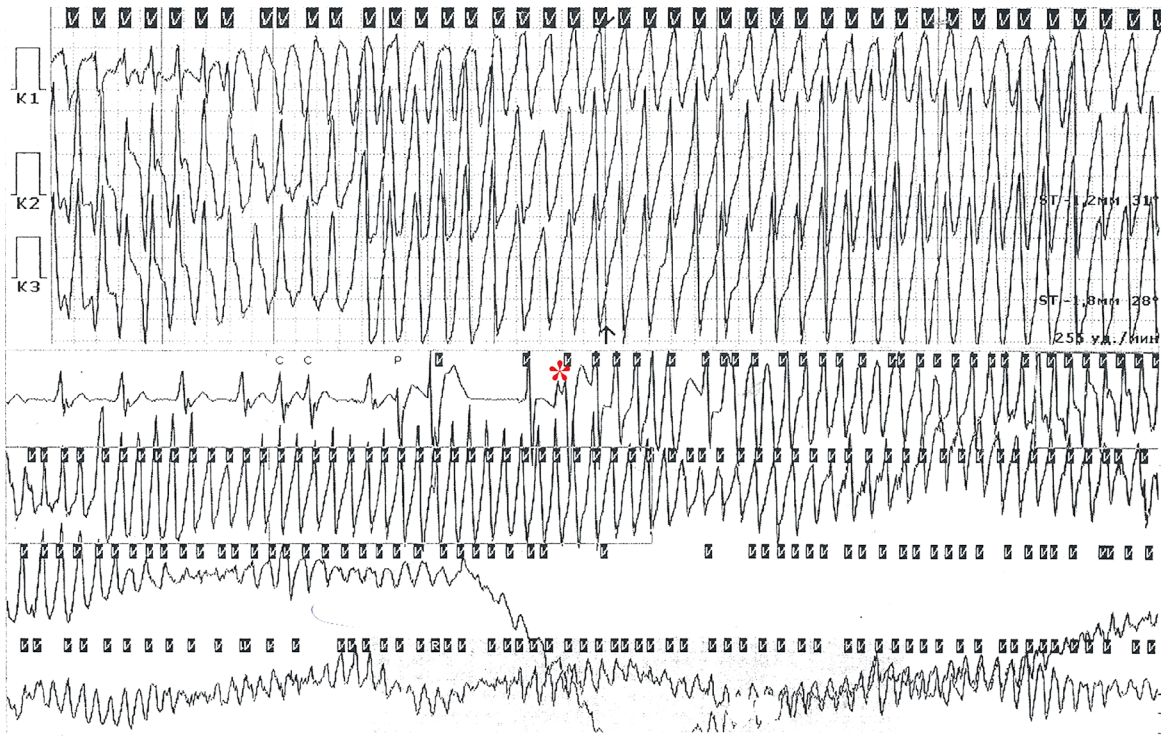

Fig. 5. 24-hour Holter ECG of patient 642c. Ventricular premature beat, *R* on *T* pattern (red asterisk), initiated a paroxysm of ventricular tachycardia with transformation into ventricular fibrillation

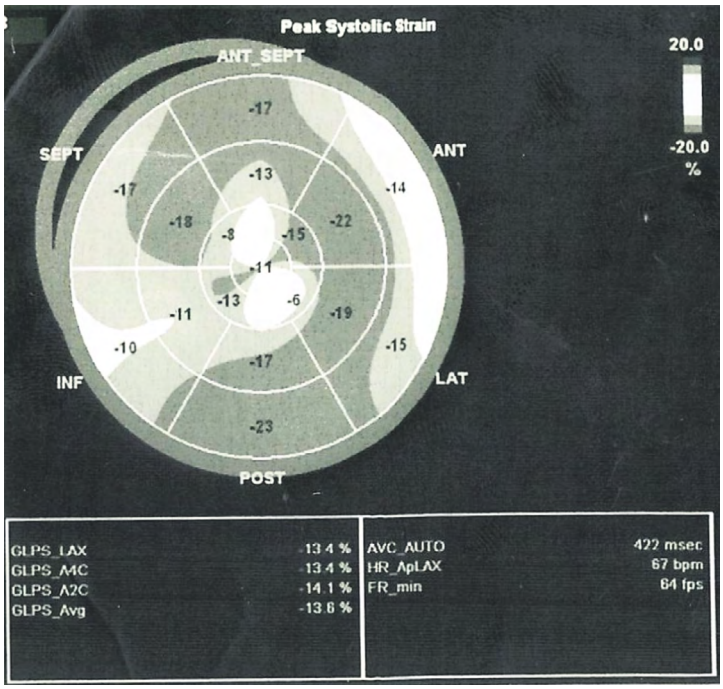

Fig. 6. 2D Speckle Tracking Echocardiography of patient 816. Left ventricular global longitudinal strain — 13,6 %

as indicated by the presence of one of the following variants: 873c, 829, 586, 543, 15m, 732, 799, 642c, 816, 868c, and 590. Pathogenic variants were identified in genes associated with LQTS, SQTS, Brugada syndrome, CPVT, and subclinical manifestations of various cardiomyopathies.

DISCUSSION

In the present study, among 20 patients initially diagnosed with IVF and UCA, the clinical diagnosis of IVF was clarified in 11 (55%) patients by genetic testing. It revealed likely pathogenic variants in the *KCNH2, SCN5A, RYR2*, and *RBM20* genes in 4 (20%) patients. In 7 (35%) patients, variants of unknown clinical significance were found in 10 genes associated with channelopathies and cardiomyopathies. No significant genetic alterations were detected in 9 (45%) out of 20 probands, although 4 had borderline *QTc* values on ECG and 2 had a family history of SCD. Apparently, the absence of genetic disorders in these patients may be due to the localization of diagnostically significant mutations in introns or in other genes not included in the research panel, or extensive deletions, the detection of which by the NGS method is challenging.

Genetic alterations associated with LQTS (30%) were common in patients with UCA, with only one patient exhibiting a mutation in the *KCNH2* gene having *QTc* prolongation up to 500 ms on one ECG series. In other patients with substitutions in the *ANK2* gene and a mutation in the *AKAP9* gene, the *QTc* interval was ⩽ 440 ms. Furthermore, the pathogenic mutation in the *CACNA1C* gene was not associated with *QTc* prolongation and other noncardiac manifestations suggestive of Timothy syndrome. Therefore, without genotyping, early diagnosis before the development of a life-threatening arrhythmic event is challenging.

The clinical phenotype of CPVT in proband 642 before age 15 years was not manifested by polymorphic nonsustained VT characteristic of this pathology, which is triggered by physical activity or emotion. Genetic testing after the development of the event revealed a mutation in the *RYR2* gene, which allowed the diagnosis to be changed to CPVT.

In two patients in whom the disease manifested with the development of VF, genotyping revealed a likely pathogenic variant in the *SCN5A* gene and substitution in the *SCN10A* gene. The spontaneous Brugada pattern was recorded on ECG at the time of the arrhythmic event with no further signs of this disorder on serial ECGs. Owing to genetic study, the diagnosis of IVF was changed to Brugada syndrome.

It is noteworthy that genotyping of patients with IVF revealed genetic variants associated with cardiomyopathies; however, the patients exhibited no obvious clinical phenotype during VF.

The results of genetic testing in patients who had UCA showed a pathogenic or likely pathogenic variant in 20% of cases. These findings demonstrate that a genetic heart disease can manifest as a life-threatening arrhythmia even in the absence of a clear clinical phenotype. Therefore, genetic testing is crucial in patients who have had UCA/IVF. The identification of a clinical phenotype in genotyped probands facilitates detection of more pathogenic variants. This is due to genetic alterations identified in the patient allow for cascade screening of family members, during which segregation analysis may confirm the pathogenicity of some variants with unknown clinical significance. Conversely, in

patients without an identifiable clinical phenotype, the test results may remain negative [17].

However, VUS remain a challenging problem in clinical practice, requiring considerable time, resources, and experience to resolve [18]. In our research, VUS were detected in 7 (35%) patients. Studies on molecular autopsy using large gene panels in investigating sudden arrhythmic death syndrome, which can be considered equivalent to UCA/IVF, showed comparable results. Nunn et al. reported that in a set of 135 genes in 59 patients with sudden arrhythmic death syndrome, 29% of patients had likely pathogenic variants and 34% had VUS [19]. Bagnall et al. reported a 27% efficiency when testing 59 genes in 113 cases of unexplained SCD [20].

Our results indicate that genetic testing is recommended for all patients with UCA, with or without evidence of cardiovascular disease. Long-term prospective studies with a large cohort of genotyped UCA patients and their families are required to determine the potential role of genetic variants in risk stratification. A better understanding of genotype–phenotype association is favorable in determining the contribution of VUS and identifying more reliable criteria for assessing pathogenicity.

CONCLUSIONS

The data from our study are intended to convey that cardiac channelopathies and subclinical manifestations of cardiomyopathies are common causes of disease in IVF patients with UCA, which require genetic testing in this group of patients. Genotyping of UCA patients revealed genetic changes associated with LQTS in 30% of cases. The *QTc* interval did not exceed 440 ms in most cases, making early diagnosis before the development of a life-threatening arrhythmic event challenging. Identifying the underlying genetic variant responsible for cardiac arrest may be beneficial in clarifying the clinical diagnosis, providing individualized treatment, and facilitating cascade screening of other at-risk family members.

STUDY LIMITATIONS

This study had several limitations. Firstly, the study sample was relatively small. Secondly, the final cohort included only patients who survived UCA referred for genetic testing. Finally, the lack of the clinical and genetic data of family members prevents a more precise interpretation of the impact of the identified variants, including those of unknown clinical significance.

ADDITIONAL INFORMATION

Ethics approval. The protocol of the study was approved by Institute of Genetics and Cytology of Belarus National Academy of Sciences Ethics Committee, protocol No. 2, 08.06.2021. Written consent was obtained from the patient for publication of relevant medical information and all accompanying images within the manuscript.

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication). Personal contribution of the authors: S.M. Komissarova — concept and design of the study, writing — original draft, patient follow-up; N.N. Chakova — conducting and interpreting the results of genetic analysis, writing — original draft; N.M. Rineiska — data curation, diagnostic studies, writing — original draft, review and editing, literature review; S.S. Niyazova — conducting and interpreting the results of the genetic analysis; T.V. Dolmatovich — conducting and interpreting the results of the genetic analysis; V.Ch. Barsukevich — patient follow-up; L.I. Plaschinskaya — diagnostic studies.

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Заключение этического комитета. Протокол исследования был одобрен этическим комитетом Института генетики и цитологии Национальной академии наук Беларуси (протокол № 2 заседания Комитета по биоэтике от 08.06.2021). Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных и фотографий.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: С.М. Комиссарова — концепция и дизайн исследования, написание текста, динамическое наблюдение за пациентами; Н.Н. Чакова — проведение и интерпретация результатов генетического анализа пациентов, написание текста; Н.М. Ринейская — анализ полученных данных, диагностические исследования, написание текста, обзор литературы; С.С. Ниязова — проведение и интерпретация результатов генетического анализа пациентов; Т.В. Долматович — проведение и интерпретация результатов генетического анализа пациентов; В.Ч. Барсукевич — динамическое наблюдение за пациентами; Л.И. Плащинская — диагностические исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

REFERENCES

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *Circulation*. 2018;138(13):e210–e271. doi: 10.1161/CIR.0000000000000548

2. Damask A, Steg PG, Schwartz GG, et al. Regeneron genetics center and the ODYSSEY OUTCOMES investigators. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. *Circulation*. 2020;141(8):624–636. doi: 10.1161/CIRCULATIONAHA.119.044434

3. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm*. 2021;18(1):e1–e50. doi: 10.1016/j.hrthm.2020.10.010

4. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10(12):1932–1963. doi: 10.1016/j.hrthm.2013.05.014

5. Iglesias M, Ripoll-Vera T, Perez-Luengo C, et al. Diagnostic yield of genetic testing in sudden cardiac death with autopsy findings of uncertain significance. *J Clin Med*. 2021;10(9):1806. doi: 10.3390/jcm10091806

6. de Noronha SV, Behr ER, Papadakis M, et al. The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths. *EP Europace*. 2014;16(6):899–907. doi: 10.1093/europace/eut329

7. Tester DJ, Medeiros-Domingo A, Will ML, et al. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing. *Mayo Clin Proc*. 2012;87(6):524–539. doi: 10.1016/j.mayocp.2012.02.017

8. Asatryan B, Schaller A, Seiler J, et al. Usefulness of genetic testing in sudden cardiac arrest survivors with or without previous clinical evidence of heart disease. *Am J Cardiol*. 2019;123(12):2031–2038. doi: 10.1016/j.amjcard.2019.02.061

9. Wilde AAM, Semsarian C, Márquez MF, et al. Developed in partnership with and endorsed by the European Heart Rhythm Association (EHRA), a branch of the European Society of Cardiology (ESC), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *Europace*. 2022;24(8):1307–1367. doi: 10.1093/europace/euac030

10. Isbister JC, Nowak N, Butters A, et al. "Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest. *Int J Cardiol*. 2021;324:96–101. doi: 10.1016/j.ijcard.2020.09.031

11. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. *J Am Coll Cardiol*. 2017;69(17):2134–2145. doi: 10.1016/j.jacc.2017.02.046

12. Mellor G, Laksman ZWM, Tadros R, et al. Genetic testing in the evaluation of unexplained cardiac arrest: From the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry). *Circ Cardiovasc Genet*. 2017;10(3):e001686. doi: 10.1161/CIRCGENETICS.116.001686

13. Visser M, Dooijes D, van der Smagt JJ, et al. Next-generation sequencing of a large gene panel in patients initially diagnosed with idiopathic ventricular fibrillation. *Heart Rhythm*. 2017;14(7):1035–1040. doi: 10.1016/j.hrthm.2017.01.010

14. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res*. 2010;38(16):e164. doi: 10.1093/nar/gkq603

15. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424. doi: 10.1038/gim.2015.30

16. Monasky MM, Micaglio E, Vicedomini G, et al. Comparable clinical characteristics in Brugada syndrome patients harboring SCN5A or novel SCN10A variants. *Europace*. 2019;21(10):1550–1558. doi: 10.1093/europace/euz186

17. Alders M, Koopmann TT, Christiaans I, et al. Haplotype-sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation. *Am J Hum Genet*. 2009;84(4):468–476. doi: 10.1016/j.ajhg.2009.02.009

18. Ackerman MJ. Genetic purgatory and the cardiac channelopathies: Exposing the variants of uncertain/unknown significance issue. *Heart Rhythm*. 2015;12(11):2325–2331. doi: 10.1016/j.hrthm.2015.07.002

19. Nunn LM, Lopes LR, Syrris P, et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing. *Europace*. 2016;18(6):888–896. doi: 10.1093/europace/euv285

20. Bagnall RD, Weintraub RG, Ingles J, et al. A prospective study of sudden cardiac death among children and young adults. *N Engl J Med*. 2016;374(25):2441–2452. doi: 10.1056/NEJMoa1510687

СПИСОК ЛИТЕРАТУРЫ

1. Al-Khatib S.M., Stevenson W.G., Ackerman M.J., et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society // Circulation. 2018. Vol. 138, N 13. P. e210–e271. doi: 10.1161/CIR.0000000000000548

2. Damask A., Steg P.G., Schwartz G.G., et al. Regeneron genetics center and the ODYSSEY OUTCOMES investigators. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial // Circulation. 2020. Vol. 141, N 8. P. 624–636. doi: 10.1161/CIRCULATIONAHA.119.044434

3. Stiles M.K., Wilde A.A.M., Abrams D.J., et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families // Heart Rhythm. 2021. Vol. 18, N 1. P. e1–e50. doi: 10.1016/j.hrthm.2020.10.010

4. Priori S.G., Wilde A.A., Horie M., et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013 // Heart Rhythm. 2013. Vol. 10, N 12. P. 1932–1963. doi: 10.1016/j.hrthm.2013.05.014

5. Iglesias M., Ripoll-Vera T., Perez-Luengo C., et al. Diagnostic yield of genetic testing in sudden cardiac death with autopsy findings of uncertain significance // J Clin Med. 2021. Vol. 10, N 9. ID 1806. doi: 10.3390/jcm10091806

6. de Noronha S.V., Behr E.R., Papadakis M., et al. The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths // EP Europace. 2014. Vol. 16, N 6. P. 899–907. doi: 10.1093/europace/eut329

7. Tester D.J., Medeiros-Domingo A., Will M.L., et al. Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing // Mayo Clin Proc. 2012. Vol. 87, N 6. P. 524–539. doi: 10.1016/j.mayocp.2012.02.017

8. Asatryan B., Schaller A., Seiler J., et al. Usefulness of genetic testing in sudden cardiac arrest survivors with or without previous clinical evidence of heart disease // Am J Cardiol. 2019. Vol. 123, N 12. P. 2031–2038. doi: 10.1016/j.amjcard.2019.02.061

9. Wilde A.A.M., Semsarian C., Márquez M.F., et al. Developed in partnership with and endorsed by the European Heart Rhythm Association (EHRA), a branch of the European Society of Cardiology (ESC), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS). European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases // Europace. 2022. Vol. 24, N. 8. P. 1307–1367. doi: 10.1093/europace/euac030

10. Isbister J.C., Nowak N., Butters A., et al. "Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest // Int J Cardiol. 2021. Vol. 324. P. 96–101. doi: 10.1016/j.ijcard.2020.09.031

11. Lahrouchi N., Raju H., Lodder E.M., et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome // J Am Coll Cardiol. 2017. Vol. 69, N 17. P. 2134–2145. doi: 10.1016/j.jacc.2017.02.046

12. Mellor G., Laksman Z.W.M., Tadros R., et al. Genetic testing in the evaluation of unexplained cardiac arrest: From the CASPER (Cardiac Arrest Survivors with Preserved Ejection Fraction Registry) // Circ Cardiovasc Genet. 2017. Vol. 10, N 3. ID e001686. doi: 10.1161/CIRCGENETICS.116.001686

13. Visser M., Dooijes D., van der Smagt J.J., et al. Next-generation sequencing of a large gene panel in patients initially diagnosed with idiopathic ventricular fibrillation // Heart Rhythm. 2017. Vol. 14, N 7. P. 1035–1040. doi: 10.1016/j.hrthm.2017.01.010

14. Wang K., Li M., Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data // Nucleic Acids Res. 2010. Vol. 38, N 16. P. e164. doi: 10.1093/nar/gkq603

15. Richards S., Aziz N., Bale S., et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology // Genet Med. 2015. Vol. 17, N 5. P. 405–424. doi: 10.1038/gim.2015.30

16. Monasky M.M., Micaglio E., Vicedomini G., et al. Comparable clinical characteristics in Brugada syndrome patients harboring SCN5A or novel SCN10A variants // Europace. 2019. Vol. 21, N 10. P. 1550–1558. doi: 10.1093/europace/euz186

17. Alders M., Koopmann T.T., Christiaans I., et al. Haplotype-sharing analysis implicates chromosome 7q36 harboring DPP6 in familial idiopathic ventricular fibrillation // Am J Hum Genet. 2009. Vol. 84, N. 4. P. 468–476. doi: 10.1016/j.ajhg.2009.02.009

18. Ackerman M.J. Genetic purgatory and the cardiac channelopathies: Exposing the variants of uncertain/unknown significance issue // Heart Rhythm. 2015. Vol. 12, N 11. P. 2325–2331. doi: 10.1016/j.hrthm.2015.07.002

19. Nunn L.M., Lopes L.R., Syrris P., et al. Diagnostic yield of molecular autopsy in patients with sudden arrhythmic death syndrome using targeted exome sequencing // Europace. 2016. Vol. 18, N 6. P. 888–896. doi: 10.1093/europace/euv285

20. Bagnall R.D., Weintraub R.G., Ingles J., et al. A prospective study of sudden cardiac death among children and young adults // N Engl J Med. 2016. Vol. 374, N 25. P. 2441–2452. doi: 10.1056/NEJMoa1510687

AUTHORS INFO

***Nadiia M. Rineiska,** MD, Cand. Sci. (Med.), researcher, Laboratory of Chronic Heart Failure, State Institution Republican Scientific and Practical Centre «Cardiology»;
address: 110, Rosa Luxemburg st., Minsk, 220036, Belarus;
ORCID: 0000-0002-1986-1367; eLibrary SPIN: 2782-2270,
e-mail: nadya.rin@gmail.com

Svetlana M. Komissarova, MD, Dr. Sci. (Med.), professor;
ORCID: 0000-0001-9917-5932; eLibrary SPIN: 8023-5308,
e-mail: kom_svet@mail.ru

Natalya N. Chakova, Cand. Sci. (Biol.);
ORCID: 0000-0003-4721-9109; eLibrary SPIN: 5682-1497,
e-mail: chaknat@mail.ru

Svetlana N. Niyazova, junior researcher;
ORCID: 0000-0002-3566-7644; eLibrary SPIN: 1093-1793,
e-mail: kruglenko_sveta@tut.by

Tatyana V. Dolmatovich, Cand. Sci. (Biol.);
ORCID: 0000-0001-7562-131X, e-mail: t.dolmatovich@igc.by

Veronika Ch. Barsukevich, MD, Cand. Sci. (Med.);
ORCID: 0000-0002-5180-7950; eLibrary SPIN: 9413-7121;
e-mail: barsukevich.v@gmail.com

Larisa I. Plashchinskaya, MD, Cand. Sci. (Med.);
ORCID: 0000-0001-8815-3543; eLibrary SPIN: 2666-1270;
e-mail: lario2001@mail.ru

ОБ АВТОРАХ

***Надежда Михайловна Ринейская,** канд. мед. наук, научный сотрудник лаборатории хронической сердечной недостаточности ГУ «РНПЦ «Кардиология»;
адрес: 220036, Республика Беларусь, Минск, ул. Розы Люксембург, д. 110Б; ORCID: 0000-0002-1986-1367;
eLibrary SPIN: 2782-2270, e-mail: nadya.rin@gmail.com

Светлана Михайловна Комиссарова, д-р мед. наук, профессор; ORCID: 0000-0001-9917-5932; eLibrary SPIN: 8023-5308,
e-mail: kom_svet@mail.ru

Наталья Николаевна Чакова, канд. биол. наук;
ORCID: 0000-0003-4721-9109; eLibrary SPIN: 5682-1497,
e-mail: chaknat@mail.ru

Светлана Сергеевна Ниязова, младший научный сотрудник;
ORCID: 0000-0002-3566-7644; eLibrary SPIN: 1093-1793,
e-mail: kruglenko_sveta@tut.by

Татьяна Владимировна Долматович, канд. биол. наук;
ORCID: 0000-0001-7562-131X, e-mail: t.dolmatovich@igc.by

Вероника Чеславовна Барсукевич, канд. мед. наук;
ORCID: 0000-0002-5180-7950; eLibrary SPIN: 9413-7121;
e-mail: barsukevich.v@gmail.com

Лариса Иосифовна Плащинская, канд. мед. наук;
ORCID: 0000-0001-8815-3543; eLibrary SPIN: 2666-1270;
e-mail: lario2001@mail.ru

* Corresponding author /Автор, ответственный за переписку